Remarks

In the interest of facilitating prosecution herein, Applicant has amended Claim 23 to recite that the adjuvant composition *consists of* an ionic polysaccharide component and a saponin component. Such amendment is solely for the purpose of facilitating the granting of claims that are directed to the immediate launch of Applicant's commercial products. Applicant believes that it is entitled to granted claims irrespective of whether the claims recite "consisting of" "consisting essentially of" or "comprising", and that any analysis to the contrary simply misses the point of the prior art of record, as understood by those who practice the art. Accordingly, Applicant will promptly file additional continuation applications directed to such additional and proper characterizations of its overall inventions.

In regard of the amendments to the text of Claims 23, 24, 25 and 27, ionic polysaccharide is defined, for example, at pages 7-8 in the PCT-origin specification. The saponin component, including that it may be Quil A is defined, for example beginning on Page 9, line 19, and continuing on through all of Page 10, wherein immunostimulatory complexes formed of saponin are also defined. That the immunostimulatory complex may comprise Quil A, cholesterol, and phosphatidyl choline is stated at Page 10, lines 13-14, and throughout the Examples. That QAE-dextran is an ionic polysaccharide component useful in the practice of the invention is recited at page 9, line 7. The limitation in Claim 23 that the mass ratio of the ionic polysaccharide component to the immunostimulating complex component is in the range of 50 to 300, has been deleted, and reappears as a limitation in new dependent claim 39.

The section 103 rejection

The Examiner has rejected Claims 23-38 under 35 USC section 103(a) under a combination of GB2,228,262, US Patent 4,900,549, and WO99/27959 (itself having US 6,528,058 as a counterpart). The rejection is respectfully traversed.

A primary feature of the present invention is to provide adjuvant compositions that facilitate the triggering of substantial immune responses against an antigen (i.e. high antibody titers), while, at the same time, not being significantly reactogenic, therefore not to cause high and lingering irritancy at the site of vaccination. Such irritancy and reactogenic properties are of course painful to vaccinated animals, and even in the case of animals soon to be slaughtered, such effects compromise carcass/meat characteristics.

According to the practice of the present invention, such non-obvious results (see Examples 5-7 in the Specification) are provided via adjuvant compositions that contain an ionic polysaccharide and an immunostimulating complex (as specially defined herein) which itself comprises a saponin and a sterol (such as cholesterol), and a phospholipid (such as phosphatidly choline) and wherein the immunostimulating complex may contain additional active components. Such features are neither present or predicted by the prior art.

Prior to addressing the specific points of the Examiner's rejection, some overall comments concerning the cited prior art references are in order.

The WO99/27959 reference is directed to trivalent adjuvant compositions which those authors state (see page 10) provide for higher antibody titers that certain cited divalent adjuvant compositions, although there may not be appropriate comparison also as to disadvantageous reactogenic properties of the various adjuvants. In any case, the compositions disclosed according to this reference invariably contain an immunoadjuvant oil as a necessary ingredient, and never contain cholesterol and phospholipid (complexed with saponin according to the practice of the present invention in the "immunostimulatory complex" to prevent the saponin from otherwise "extracting" native cholesterol molecules from cell membranes thus causing localized tissue damage at the injection site). Therefore, it is difficult to imagine how this reference is to be combined with any other teachings, in order to provide a proper section 103 rejection, absent a specific teaching *from some other reference* that the essential ingredient (adjuvating oil) of WO99/27959 is NOT to be used after all.

The GB 2 228 262 publication is solely directed to LHRH (or LHRH analog) conjugates which may be further coupled to DT, for example. However, the present Applicant does not claim to be the first inventive entity to have ever coupled LHRH to DT, and present claim 23 is not limited in any way as to the antigen which is delivered with the adjuvant composition therewith, therefore the overall relevance of the cited publication to the present invention seems quite remote.

In regard of US 4,900, 549 (and there are other references which report similar technology), and although the reference is directed to providing "immunostimulatory complexes", there is no teaching at all in this reference that the adjuvant can be improved (i.e. to provide a preferred combination of high immunizing activity and reduced

reactogenicity) by replacing some of the saponin/immunostimulatory complex with ionic polysaccharide. Rather, that is the discovery of the present invention. As previously mentioned, this missing teaching is clearly not to be provided by WO99/27959, which *invariably* instructs to also use an adjuvating oil, all the while the saponin is not formed into an immunostimulatory complex (with cholesterol and phospholipid), as the present application (and claims) so define.

Therefore, in regard of how all such teachings might be combined, the following further comments are of note.

Applicant does not understand the purpose of the citation to GB 2,228,262, since most of what is taught according to the practice of that invention is simply not present according to the practice (independent claim 23) of the present invention, and the present Applicant does not include alum as an adjuvant at all. Indeed, the Examiner acknowledges that everything that is the present in Applicant's adjuvant is actually physically missing from that reference (see Page 2, numbered Para 5 of the Official Action of February 17, 2009).

Applicant respectfully disagrees with the Examiner's assertion that the WO99/27959 reference teaches (again see Page 2, numbered Para 5, of the aforementioned Official Action) that DEAE-dextran and Quil A are a synergistic combination, since the actual disclosed compositions also require oil as additional adjuvant to achieve this apparent synergy [a concept which is invariably avoided in all Office discussions], and the very text of the publication states that the specifically-identified 3 component adjuvant systems work better than 2 component systems. There is simply no statement or data to the contrary. Further, there is no mention of the value of cholesterol and phospholipid as added components, to first place the saponin in an immunostimulatory complex, and also to minimize saponin-triggered cell damage. Therefore, the combination of WO99/27959 and GB 2,228,262 simply does not suggest the present invention.

To the extent that the '549 patent is supposed to bridge this deficiency, it is noteworthy that the February 17, 2009 Official Action only devotes 2 lines of text to this bridging (see Page 3), and no discussion is presented (either in the references or the Official Action) as to why those skilled in the art should, first, simply disregard of the teaching of the obligate adjuvant oil component in WO99/27959, and second, proceed to add highly reactogenic ionic polysaccharide adjuvants to less reactogenic adjuvants (the

immunostimulatory complexes or Iscoms of the '549 Patent) and for what purpose. Rather, it reasonably appears that the Examiner is simply engaging in hindsight reconstruction of the present invention which provides high immunogenicity without reactogenicity. To the extent that the Examiner has found all of the components, themselves, in the prior art, is to say nothing more than all chemical inventions are obvious unless they rely on a chemical element not already in the Periodic Table of the Elements.

The mere existence of the various components of the present invention -- as separate components in the separate prior art citations -- is not the same as the motivation to combine them. And notwithstanding that the teaching of effectiveness in the WO99/27959 publication is actually and clearly related to the oil-containing, 3-component adjuvant and not a 2-component (Quil A and DEAE-dextran) adjuvant [as reported on Page 5 of the February 17, Official Action], there simply remains the requirement that the references must be considered for the totality of what they teach, and not for any convenient bits and pieces of information therein. The teaching of the WO99/27959 publication is simply that cholesterol-free saponin systems can be improved by adding ionic polysaccharide, but only if adjuvating oil is also present.

Fundamentally, the Patent Office cannot pick and choose which among all the items of information in the respective references are to be exploited, and which teachings (or lack of teachings) are to be conveniently disregarded, in an attempt to reconstruct the present Applicant's invention. Thus, it is impossible to read the references, *in their entirety*, to suggest that one should make a saponin-ionic polysaccharide system, but that you should certainly add cholesterol and phospholipid, and certainly leave out any adjuvating oil.

On this basis, Applicant respectfully directs attention to the paragraph bridging pages 4-5 of the Final Action of December 3, 2009, and to the similar paragraph which concludes the Advisory Action of March 17, 2010 (as it refers therein Page 2, lines 14-16 of the cited WO 99/27959 reference), which cited text, rather than referring to the subject matter of the '959 reference, refers only to aspects of the earlier disclosures of others. Applicant would rather direct attention to Page 2, lines 14-19 of the WO 99/27959 reference.

"Among other adjuvants which have been or are currently used are the saponins, particularly tripterpenoid mixtures, such as Quil A (a purified extract from the bark of the tree Quillaja saponarioa) in aqueous solution or in the form of a matrix with cholesterol.

Polycations such as diethylaminoethyldextan (DEAE dextran) can also be effective as adjuvants in *some* [emphasis added] cases" And what are these cases?

Rather, a careful reading of the '959 specification shows that those authors do not suggest combining saponins and ionic polysaccharides unless there is a mineral oil which must also be invariably present as an additional adjuvant. And there is clearly no teaching in the '959 patent that -- absent the presence of mineral oil -- that the 2-component adjuvant would be effective and safe. Again, where saponin and ionic polysaccharide are actually disclosed for use in the '959 specification, mineral oil is always present. That is the actual teaching of the '959 specification. Additionally cholesterol is always absent, as is certainly also phospholipid and any (optional) additional protein, all of which are needed to make an "immunostimulatory complex", as claimed herein.

Additionally, the Advisory Action states (last paragraph) " Note that the '959 publication *does not exclude* cholesterol in the composition comprising a saponin". [emphasis added] It thus reasonably appears that the Examiner is impermissibly introducing hypothetical issues of infringement (which is not the jurisdiction of the Patent Office) into the needed analysis of patentability. **Or stated differently, the present Applicant's claims are not being rejected over what is actually in the '959 reference, they are being rejected over what is not in the reference, or any other reference. And what is the statutory basis for being rejected over what is not in a reference?**

Therefore, Applicant's invention is both novel and non-obvious, and Applicant's arguments are not misleading.

Conclusion

The Examiner is welcome to contact the undersigned to facilitate further prosecution. A Request for Continued Examination (RCE) Transmittal is attached in duplicate and a Petition for Extension of Time is also attached in duplicate. The Patent Office is authorized to charge any needed fees or fee amounts to Applicant's Deposit Account, No. 16-1445. An early and favorable action is respectfully requested.

Respectfully submitted,

Date: 12/13/10

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